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(54) Composition for cosmetic, pharmaceutical or dietetic use based on an amino-sugar and/ or a polyhydroxylic acid

(57) A composition for cosmetic, pharmaceutical or dietetic use and including as the active ingredient, at least one of the substances which include acetylglucosamine and glucuronic acid in combination with the

active ingredients which belong to the chemical class of the carboxylic acids,  $\alpha$ -hydroxy acids, vitamins, amino acids, and bioflavonoids, and formulated with particular synergists, additives, and excipients for external use or for internal use.

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**Description**

The object of the present invention is a novel composition for cosmetic, pharmaceutical or dietetic use that is essentially intended for external use to be applied either on intact or injured skin, or on the mucous membranes, and for internal use, taken in the form of tablets, delayed-action tablets, capsules, syrup, drops, suppositories or in any other pharmaceutical form intended for the taking of the drug orally, or injected intramuscularly, intravenously, subcutaneously, intra-articularly or in any other form intended for the administration of the composition in question by means of injection.

More specifically, the present invention pertains to a composition for the above-mentioned use, which is characterized in that it contains, as the active ingredient, at least one of the substances which include acetylglucosamine and glucuronic acid in combination with the active ingredients which belong to the chemical class of the carboxylic acids,  $\alpha$ -hydroxy acids, vitamins, amino acids, and bioflavonoids, and formulated with particular synergists, additives, and excipients for external use or for internal use.

Acetylglucosamine and glucuronic acid may, by way of indication, also be described as precursors of the glycosaminoglycans.

The stimulation of the biosynthesis or even the simple supply of suitable biochemical precursors, which may be described, from a purely chemical point of view, as molecular elements that, alone or combined, constitute the monomers or the parts of the monomers of the various polysaccharide structures, specifically the glycosaminoglycans, which can constitute the polysaccharide fraction of the proteoglycan structures, produces beneficial biological effects on the treatment of the skin against the effects of aging and for the course of treatment of the various conditions of the skin, of the joints, and the like.

The purpose of the present invention is precisely to provide a cosmetic, pharmaceutical, or dietetic composition, which is able to develop and to sustain even such biological effects, among others, containing mainly acetylglucosamine and glucuronic acid in combination with the active ingredients belonging to the chemical class of the carboxylic acids,  $\alpha$ -hydroxy acids, vitamins, amino acids, flavonoids, and polysaccharides.

By way of indication, the effects that may be achieved are direct and are expressed as:

- biological, physiological, chemical, physical, pharmacological action by the acetylglucosamine and the glucuronic acid either alone or combined;
- a biological, physiological, chemical, physical, or pharmacological action of the polysaccharide and/or proteoglycan molecular structures obtained by means of the stimulation of the endogenous biosynthesis starting from the molecular structures of the acetylglucosamine and of the glucuronic acid, either alone or combined;

or the effects are indirect and are expressed as:

- biological, physiological, chemical, physical, or pharmacological action of the polysaccharide molecular structures obtained by means of the stimulation of the endogenous biosynthesis of the molecular structures of the glycosaminoglycans and of the proteoglycans, with other molecular or macromolecular structures present in the human body with which they would or may interact.

For their synthesis, some glycosaminoglycans have an active metabolite that is basically represented by UDP-N-acetylglucosamine, which has a precursor in acetylglucosamine.

Acetylglucosamine belongs to the class of amino sugars, and is widespread in nature in the form of repetitive polymers of the same molecular unit to form complex structures, such as chitin, and constitutes one of the two molecular fractions which form the monomer of the various glycosaminoglycans, including hyaluronic acid.

Glucuronic acid, joined with acetylglucosamine by a 1-4- $\beta$ -glycosidic bond, forms the monomer of hyaluronic acid. Thus, glucuronic acid acts as a precursor of hyaluronic acid either alone or combined with the acetylglucosamine.

Acetylglucosamine and glucuronic acid have the property of preventing the hyperoxidative phenomena, which, among other things, may have an effect on the macromolecules of a polysaccharide nature, e.g., the hyaluronic acid.

However, by way of indication and not exhaustively, the action exerted by the acetylglucosamine and by the glucuronic acid towards the stimulation of the biosynthesis of the glycosaminoglycans and the proteoglycans and, consequently, the multiphasic and multicentric action of the identical glycosaminoglycans and proteoglycans on the skin, on the joint zones and on the other organic regions are combined.

The therapeutic role played by acetylglucosamine, by glucuronic acid, and by their interaction thus appears to be clear in all those pathological forms, in which it becomes necessary to stimulate the endogenous production, e.g., of hyaluronic acid.

In the field of cosmetics, since a reduction in the amount of hyaluronic acid present in the skin occurs during aging, with resulting dehydration of the skin, appearance of wrinkles and loss of elasticity and of tonicity of the skin, the action

in the various weight ratios described below.

When present, these substances may be contained in amounts of 0.001 to 10 wt.%, and preferably of 0.05 to 1 wt.% when the proportions of acetylglucosamine and/or glucuronic acid are each from 0.05 to 15 wt.%.

The composition of the present invention may also contain plants, extracts of plant or parts of plants or their extracts, including roots, leaves, fruits, bark, flowering top, in the form of dry, soft or liquid extracts.

The following may be mentioned as examples of these synergists: *Silybum Marianum*, *Echinacea Angustifolia*, *Aesculus Hippocastanum*, *Calendula Officinalis*, *Centella Asiatica*, *Hamamelis Virginiana*, *Vaccinium Myrtillus*, *Citrus Aurantium Amara*, *Citrus Aurantium Dulcis*, *Citrus Limonium*, *Equisetum Arvense*, *Glycrrhiza Glabra*, *Aloe Vera*, *Ruta Graveolans*, *Vitis Vinifera* used alone or combined.

The presence of these synergists may be 0.001 to 30 wt.%, and preferably 0.25 to 20 wt.% when acetylglucosamine and/or glucuronic acid are each contained in amount of 0.05 to 15 wt.%.

The composition of the present invention may also contain, either alone or in combination, chemical substances that may be terpenes, triterpenes, saponins, isoflavonoids, alcohol flavonoids, and the like.

*Anthocyanidins* of the bilberry, escin, madecassic acid, madecassosides, asiaticosides, asiatic acid, rutin and its derivatives, including the salts and esters thereof, diosmin, sericic acid, sericosides, echinacosides, echinacin, glyceretic acid and its salts or esters, quercitin, isoquercitin, bisabolene, silymann, cyanidins, leucocyanidins, although contained in plant extracts or plant parts (including leaves, roots, fruits, bark) and the corresponding salts or esters, may be mentioned as examples of these substances.

These substances may be contained in an amount of 0.01 to 20 wt.%, and preferably from 0.05 to 15 wt.%.

The composition of the present invention may contain, alone or combined, substances belonging to the chemical class of amino acids selected from among: alanine, arginine, aspartic acid, asparagine, cysteine, glutamic acid, glutamine, glycine, histidine, leucine, isoleucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, the corresponding salts and esters and the various forms reduced to amino alcohols, both in dextrorotatory and levorotatory form and the related racemic mixtures.

These substances may be contained in amounts of 0.001 to 20 wt.%, and preferably from 0.05 to 15 wt.% when the acetylglucosamine and/or the glucuronic acid are each contained in amounts of 0.05 to 15 wt.%.

The composition of the present invention may contain, alone or combined, substances belonging to the chemical class of the polysaccharides, including hyaluronic acid, chitin, chitosan, dermatan sulfate, and heparin. These substances may be contained in amounts of 0.0001 to 20 wt.%, and preferably from 0.05 to 5 wt.% when the acetylglucosamine and/or the glucuronic acid are each contained in amounts of 0.05 to 15 wt.%.

The combination of acetylglucosamine, of glucuronic acid, or of both with suitable synergists proves to be innovative in the field of cosmetics in dealing with various phenomena associated with the degeneration of aesthetic parameters of the skin. It is particularly useful, but not exclusively, for a moisturizing action, an anti-aging action, anti-wrinkle action, elasticizing action, hardening action, anti-cellulitis action, the cosmetic treatment of baldness, the cosmetic treatment of teleangiectasia and of blotchiness.

Its use is also innovative in the pharmaceutical field for the topical treatment of atopic dermatitides, seborrheic dermatitides, nummular eczematous dermatitides, exfoliative dermatitides, stasis dermatitides, neurodermatitides, acne, acne rosacea, cicatricial alopecia, hippocratic alopecia, female-pattern alopecia, drug-induced alopecia, alopecia areata, pseudofolliculitis, psoriasis, lichen ruber planus, ichthyosis, xeroderma, keratosis pilaris, decubitus ulcers, trophic ulcers, torpid sores, vascular spider angiomas, hemangiomas, telangiectatic granuloma, seborrheic keratosis, fibrous histiocytoma, morpha, the treatment of hypertrophic scars, burn scars, teleangiectasia, changes in the circulation and the microcirculation, venous stasis, circulatory stasis, lupus erythematosus, topical treatment of scleroderma, and healing of wounds.

The composition of the present invention, which contains acetylglucosamine and/or glucuronic acid optionally with other active ingredients, vitamins, and various additives, may be prepared in formulations for external use, as water-in-oil emulsions, oil-in-water emulsions, monophasic solutions, biphasic pseudo solutions, monophasic gels, biphasic gels or submicellar gels, anhydrous salves, dusting powders, etc., or for internal use, as capsules, tablets, drops, syrups, intramuscular, intravenous, subcutaneous, or intra-articular injections, etc., using the appropriate supports or vehicles.

The composition of the present invention may also be effectively used for internal use in the pharmaceutical field, e.g., in the treatment of degenerative forms of the amorphous component of tissues, circulatory stasis, venous stasis, rheumatoid arthritis, osteoarthritis, arthrosis, scleroderma, etc.

The following preparation examples are further illustrative of and, in the cases specified, descriptive of the composition of the present invention.

In these examples, the proportions, if not indicated otherwise, are in weight percent based on the final composition.

exerted by acetylglucosamine, by glucuronic acid and by the related combination is of considerable importance.

In addition, the action of the glycosaminoglycans, whose production may be stimulated by the acetylglucosamine and by the glucuronic acid, either alone or combined, also involves, among other things, the other structures of the skin, such as the collagens, the elastic fibers, and the structural proteins, so that a stimulation by means of the above-mentioned biochemical precursors of the glycosaminoglycans and of the proteoglycans of the amorphous matrix of the skin leads to aesthetically and pharmacologically relevant results.

The action exerted by the acetylglucosamine and by glucuronic acid, either alone or combined, with other active ingredients of a flavonoid nature either in the pure form or contained in extracts of plants or fruits or of parts of plants also proves to be particularly important in fighting against the problems which are associated with the biological, physiological, as well as physiopathological or pathological regression of the circulation and of the microcirculation.

In fact, it appears to be justified to consider, besides parietal factors, the existence of extraparietal factors, which may interfere with many functional aspects of the wall of a vessel, both in physiological conditions and especially in pathological conditions.

In fact, it is fair to believe that not only the permeability of the small vessels, but also the parietal reactive aspects are conditioned by the molecular integrity of complex glycosaminoglycans and/or proteoglycans of the perivascular interstitium.

The action that is exerted by the acetylglucosamine and by glucuronic acid with other active ingredients belonging to the class of either monocarboxylic or bicarboxylic  $\alpha$ -hydroxy acids also proves to be particularly important in improving the conditions of skin hydration either in the presence of changes of a physiological nature or of a physiopathological or pathological nature.

In case of application for topical use, the keratolytic action exerted by the promotes the absorption of the acetylglucosamine and of the glucuronic acid, making possible a better bioavailability of the two active ingredients and thus a more marked stimulating action on the biosynthesis of the glycosaminoglycans.

The combination of acetylglucosamine and glucuronic acid with hyaluronic acid (in the polymer form) also proves to be particularly positive in the case of subcutaneous or intradermal use.

In fact, the use of hyaluronic acid injected in the dermis, thanks to its property of holding considerable amounts of water, makes it possible to raise the skin, reducing the presence of wrinkles thanks to a physical type action.

Since the hyaluronic acid injected intradermally is degraded in relatively short times, the endogenous, stimulating action of hyaluronic acid performed by acetylglucosamine and by glucuronic acid appears to be justified.

The various features of novelty which characterize the invention are pointed out with particularity in the claims annexed to and forming a part of this disclosure. For a better understanding of the invention, its operating advantages and specific objects attained by its uses, reference is made to the accompanying descriptive matter in which preferred embodiments of the invention are illustrated.

When used alone, the acetylglucosamine may be contained in the composition in an amount of 0.01 to 30 wt.%, and preferably from 0.05 to 15 wt.%, based on the final formulation.

When used alone, the glucuronic acid may be contained in the composition in an amount of 0.001 to 20 wt.%, and preferably from 0.05 to 30 wt.%, based on the final formulation.

When used combined, the acetylglucosamine and the glucuronic acid (or the glucuronolactone) may be contained in the composition in an amount of 0.0001 to 50 wt.% each, and preferably in an amount equal to 0.05 to 15 wt.% each.

In addition, the composition based on acetylglucosamine and/or glucuronic acid may contain various active ingredients, which we will define as synergists for descriptive simplicity.

The synergists may be selected from the group comprising carboxylic acids,  $\alpha$ -hydroxy acids and  $\beta$ -hydroxy acids, either monocarboxylic or bicarboxylic.

Glycolic acid, lactic acid, hydroxybutyric acid, mandelic acid, tartaric acid, malic acid, salicylic acid, hydroxybenzoic acid, citric acid, lipoic acid (thioctic acid), either in the oxidized or reduced form, intended both in the dextrorotatory and levorotatory forms, as well as the racemic mixtures and the corresponding salts, esters or amides, may be mentioned as examples.

Two or more of these synergists may be present in the composition, alone or combined, together with the acetylglucosamine and/or the glucuronic acid.

Such synergists may be contained in amounts ranging from 0.001 to 50 wt.%, and preferably from 0.5 to 15 wt.%, based on the final formulation when the proportions of the acetylglucosamine and/or of the glucuronic acid are each 0.05 to 15 wt.%.

In addition, the composition of the present invention may contain either liposoluble or water-soluble vitamins.

Examples are: vitamin B1 (thiamin), vitamin B2 (riboflavin), vitamin B6 (or pyridoxin, pyridoxal, pyridoxamine), niacin (nicotinic acid, nicotinic amide), pantothenic acid, biotin, folic acid (folic acid, folinic acid), vitamin E (tocopherol), vitamin C (ascorbic acid), beta carotene, retinol (vitamin A), retinal, retinoic acid, para-aminobenzoic acid (4-aminobenzoic acid), vitamin F (linoleic acid), vitamin F (linolenic acid), vitamin F (arachidonic acid), vitamin P (rutin), in both the dextrorotatory and levorotatory forms, as well as the related racemic mixtures, and the corresponding salts or esters

## Preparation Example 2 (Cosmetic Use)

Multilamellar-based. Crystalline. Liquid Emulsion Containing Acetylglucosamine. Glucuronic Acid and Silymarin. Tocopherol

- 5 This is a structured oil-in-water emulsion in the form of a multilamellar, crystalline, liquid phase, which is mainly indicated to deal with the problems associated with the typical problems of skin, which is sensitive and can easily turn red, and with problems of the formation of teleangiectasias.
- 10 The present formulation has a marked antioxidant effect, which is able to prevent or hinder the phenomena linked with aging of the skin.
- 15 The present formulation also proves to be indicated for hindering the symptoms of acne rosacea, mainly but not exclusively in the initial clinical stages.
- The formation of the multilamellar, crystalline liquid phase inside the emulsion is obtained by means of an accurate calibration of a ternary system (x) and by a pentenary system (y), which are represented by three cetyl or stearyl type emulsifying agents and by five chemical entities of a lipid nature, either solid or liquid, also cetyl or stearyl typ . re-
- 20 spectively.
- The particular method of preparation, together with types of ingredients used, makes it possible to obtain a mesomorphic phase, in which a multilamellar, crystalline liquid phase with the molecular property of the solid phas and the mobility property of the liquid phase is formed on the surface of the oil micelles.
- 25 This particular chemical-physical configuration of the emulsion proves to be visible by means of analysis using polarized-light microscopy.
- The structured emulsion in the form of a multilamellar, crystalline liquid phase makes it possible to amplify the action of the product over time, to act as a "reservoir" of active ingredients, proves to be useful in the protection of the active ingredients used, and increases the stability of the emulsion.
- 30 Thus, the calibrated combination of acetylglucosamine, of glucuronic acid, of silymarin and of tocopherol, which are structured in a multilamellar-based, crystalline liquid emulsion, represents an innovation that is able to yield remarkable results.

Water-in-oil Emulsion			
PHASE (A)	Amount in wt. %		
	From	To	
1. STEARETH-2	0.500	4.000	(x)
2. CETEARYL GLUCOSIDE	0.200	6.000	(x)
3. PPG-15-STEARYL ETHER	6.000	12.500	(y)
4. STEARETH-21	0.100	6.400	(x)
5. CETYL ALCOHOL	0.750	6.100	(y)
6. STEARIC ACID	0.100	7.800	(y)
7. CETEARYL ALCOHOL	0.100	5.600	(y)
8. CETEARYL OCTANOATE	0.200	4.000	(y)
9. TOCOPHERYL ACETATE	0.100	7.000	
10. PHASE (B)			
11. ACETYLGLOUCOSAMINE	0.100	7.900	
12. D-GLUCURONIC ACID GAMMA LACTONE	0.100	7.900	
13. WATER qs.	5.000	5.000	
14. PHASE (C)			
15. SILYMARIN	0.100	4.750	
16. WATER qs.	100	100	

## Method of Preparation:

- 55 6. Heat phase A) to +80°C and then heat phase C) to +72°C. Combin phas C) with phase A) and homogenize for 15 minutes at 2.500 rpm, under agitation and aspirated vacuum.

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The Use of the Composition in the Form of an Emulsion Obtained by Means of Preparation Example 1 (Cosmetic and/or Pharmaceutical Use) Multilamellar-based. Crystalline. Liquid Emulsion Containing Acetylglucosamine. Glucuronic Acid and Diosmin

5 This is a structured oil-in-water emulsion in the form of a multilamellar, crystalline, liquid phase, which is mainly indicated to deal with the problems associated with deficits of a circulatory nature either in the veins or in the micro-circulation (capillaries), which can be used either in the pharmaceutical field or in the field of cosmetics (by way of indication, but not exhaustively, for the treatment of liposclerosis, commonly defined cellulitis, heaviness of the legs, teleangiectasias of various origins and locations).

10 The formation of the multilamellar, crystalline liquid phase inside the emulsion is obtained by means of an accurate calibration of a ternary system (x) and by a pentenary system (y), which are represented by three cetyl or stearyl type emulsifying agents and by five chemical entities of a lipid nature, either solid or liquid, also cetyl or stearyl type, respectively.

15 The particular method of preparation, described below together with types of ingredients used, makes it possible to obtain a mesomorphic phase, in which a multilamellar, crystalline liquid phase with the molecular property of the solid phase and the mobility property of the liquid phase is formed on the surface of the oil micelles.

This particular chemical-physical configuration of the emulsion proves to be visible by means of analysis using polarized-light microscopy.

20 The structured emulsion in the form of a multilamellar, crystalline liquid phase makes it possible to amplify the action of the product over time, to act as a "reservoir" of active ingredients, proves to be useful in the protection of the active ingredients used, and increases the stability of the emulsion.

Thus, the calibrated combination of acetylglucosamine, of glucuronic acid and diosmin, which are structured in a multilamellar-based, crystalline liquid emulsion, represents an innovation that is able to yield remarkable results.

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Water-in-oil Emulsion			
PHASE (A)	Amount in wt. %		
	From	To	
1. STEARETH-2	0.500	4.000	(x)
2. CETEARYL GLUCOSIDE	0.200	6.000	(x)
3. PPG-15-STEARYL ETHER	6.000	12.500	(y)
4. STEARETH-21	0.100	6.400	(x)
5. CETYL ALCOHOL	0.750	6.100	(y)
6. STEARIC ACID	0.100	7.800	(y)
7. CETEARYL ALCOHOL	0.100	5.600	(y)
8. CETEARYL OCTANOATE	0.200	4.000	(y)
9. PHASE (B)			
10. ACETYLGLUCOSAMINE	0.100	7.900	
11. D-GLUCURONIC ACID GAMMA LACTONE	0.100	7.900	
12. WATER qs.	5.000	5.000	
13. PHASE (C)			
14. DIOSMIN	0.100	4.750	
15. WATER qs.	100	100	

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Method of Preparation:

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1. Heat phase A) to +80°C and then heat phase C) to +72°C. Combine phase C) with phase A) and homogenize for 15 minutes at 2.500 rpm, under agitation and aspirated vacuum.
2. Initiate a slow cooling with a reduction of 2.5°C every 4 minutes.
3. At +45°C, homogenize at 3.000 rpm for 7 minutes continually under agitation.
4. At +40°C, add phase B) under agitation and allow to cool to a temperature of 30°C, continually under agitation.
5. Upon reaching 30°C, homogenize for 10 minutes at 2.000 rpm.

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11. Heat phase A) to +80°C and then heat phase C) to +72°C. Combine phase C) with phase A) and homogenize for 15 minutes at 2.500 rpm. under agitation and aspirated vacuum.
12. Initiate a slow cooling with a reduction of 2.5°C every 4 minutes.
13. At +45°C. homogenize at 3.000 rpm for 7 minutes continually under agitation.
14. At +40°C. add phase B) under agitation and allow to cool to a temperature of 30°C. continually under agitation.
15. Upon reaching 30°C. homogenize for 10 minutes at 2.000 rpm.

**Preparation Example 4 (Cosmetic and/or Pharmaceutical Use)**

**10 Multilamellar-based. Crystalline. Liquid Emulsion Containing Acetylglucosamine. Glucuronic Acid. Sericic Acid**

This is a structured oil-in-water emulsion in the form of a multilamellar. crystalline. liquid phase. which is mainly indicated to deal with the problems associated with the healing process of a wound and/or of a sore.

**15** The present formulation has a marked effect that is able to improve the aesthetic quality of the scar. The present formulation proves to be indicated for protecting the scar from the damages caused by solar radiation if either chemical or physical sun filters are added to the formulation.

**20** The formation of the multilamellar. crystalline liquid phase inside the emulsion is obtained by means of an accurate calibration of a ternary system (x) and by a pentenary system (y), which are represented by three cetyl or stearyl type emulsifying agents and by five chemical entities of a lipid nature. either solid or liquid. also cetyl or stearyl type. respectively.

The particular method of preparation. together with types of ingredients used. makes it possible to obtain a mesomorphic phase. in which a multilamellar. crystalline liquid phase with the molecular property of the solid phase and the mobility property of the liquid phase is formed on the surface of the oil micelles.

**25** This particular chemical-physical configuration of the emulsion proves to be visible by means of analysis using polarized-light microscopy.

The structured emulsion in the form of a multilamellar. crystalline liquid phase makes it possible to amplify the action of the product over time. to act as a "reservoir" of active ingredients. proves to be useful in the protection of the active ingredients used. and increases the stability of the emulsion.

**30** Thus. the calibrated combination of acetylglucosamine. of glucuronic acid. and of sericic acid. which are structured in a multilamellar-based. crystalline liquid emulsion. represents an innovation that is able to yield remarkable results.

Water-in-oil Emulsion			
PHASE (A)		Amount in wt.%	
		From	To
<b>35</b>	1.		
	2. STEARETH-2	0.500	4.000 (x)
	3. CETEARYL GLUCOSIDE	0.200	6.000 (x)
	4. PPG-15-STEARYL ETHER	6.000	12.500 (y)
<b>40</b>	5. STEARETH-21	0.100	6.400 (x)
	6. CETYL ALCOHOL	0.750	6.100 (y)
	7. STEARIC ACID	0.100	7.800 (y)
	8. CETEARYL ALCOHOL	0.100	5.600 (y)
<b>45</b>	9. CETEARYL OCTANOATE	0.200	4.000 (y)
	10. TITANIUM DIOXIDE	10.000	35.000
	PHASE (B)		
<b>50</b>	11. ACETYLGLUCOSAMINE	0.100	7.900
	12. D-GLUCURONIC ACID GAMMA LACTONE	0.100	7.900
	13. WATER qs.	5.000	5.000
	PHASE (C)		
<b>55</b>	14. SERICIC ACID	0.010	6.750
	15. WATER qs.	100	100

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7. Initiate a slow cooling with a reduction of 2.5°C every 4 minutes.
8. At +45°C. homogenize at 3.000 rpm for 7 minutes continually under agitation.
9. At +40°C. add phase B) under agitation and allow to cool to a temperature of 30°C. continually under agitation.
10. Upon reaching 30°C. homogenize for 10 minutes at 2.000 rpm.

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**Preparation Example 3 (Cosmetic and/or Pharmaceutical Use)**

Multilamellar-based. Crystalline. Liquid Emulsion Containing Acetylglucosamine. Glucuronic Acid. Asiatic Acid. Proline

10 This is a structured oil-in-water emulsion in the form of a multilamellar. crystalline. liquid phase. which is mainly indicated to deal with the problems associated with the degeneration of the elastic characteristics of the skin.

The present formulation has an effect that is able to hinder the formation of hypertrophic scars and keloids.

The present formulation also proves to be indicated for improving the healing of skin lesions.

15 The formation of the multilamellar. crystalline liquid phase inside the emulsion is obtained by means of an accurate calibration of a ternary system (x) and by a pentenary system (y), which are represented by three cetyl or stearyl type emulsifying agents and by five chemical entities of a lipid nature. either solid or liquid. also cetyl or stearyl type respectively.

20 The particular method of preparation. together with types of ingredients used. makes it possible to obtain a mesomorphic phase. in which a multilamellar. crystalline liquid phase with the molecular property of the solid phase and the mobility property of the liquid phase is formed on the surface of the oil micelles.

This particular chemical-physical configuration of the emulsion proves to be visible by means of analysis using polarized-light microscopy.

25 The structured emulsion in the form of a multilamellar. crystalline liquid phase makes it possible to amplify the action of the product over time. to act as a "reservoir" of active ingredients. proves to be useful in the protection of the active ingredients used. and increases the stability of the emulsion.

Thus. the calibrated combination of acetylglucosamine. of glucuronic acid. of proline. and of asiatic acid. which are structured in a multilamellar-based. crystalline liquid emulsion. represents an innovation that is able to yield remarkable results.

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**Water-in-oil Emulsion**

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PHASE (A)	Amount in wt. %	
	From	To
1. STEARETH-2	0.500	4.000 (x)
2. CETEARYL GLUCOSIDE	0.200	6.000 (x)
3. PPG-15-STEARYL ETHER	6.000	12.500 (y)
4. STEARETH-21	0.100	6.400 (x)
5. CETYL ALCOHOL	0.750	6.100 (y)
6. STEARIC ACID	0.100	7.800 (y)
7. CETEARYL ALCOHOL	0.100	5.600 (y)
8. CETEARYL OCTANOATE	0.200	4.000 (y)
9. PHASE (B)		
10. ACETYLGLUCOSAMINE	0.100	7.900
11. D-GLUCURONIC ACID GAMMA LACTONE	0.100	7.900
12. PROLINE	0.050	6.000
13. WATER qs.	5.000	5.000
14. PHASE (C)		
15. ASIATIC ACID	0.010	4.750
16. PROPYLENE GLYCOL	2.000	6.000
17. WATER qs.	100	100

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**Method of Preparation:**

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16. Heat phase A) to +50°C and then heat phase C) to +72°C. Combine phase C) with phas A) and homogenize for 15 minutes at 2.500 rpm. under agitation and aspirated vacuum.
17. Initiate a slow cooling with a reduction of 2.5°C every 4 minutes.
18. At +45°C. homogenize at 3.000 rpm for 7 minutes continually under agitation.
19. At +40°C. add phase B) under agitation and allow to cool to a temperature of 30°C. continually under agitation.
20. Upon reaching 30°C. homogenize for 10 minutes at 2.000 rpm.

**Preparation Example 5 (Cosmetic Use)**

**10 Multilamellar-based. Crystalline. Liquid Emulsion Containing Acetylglucosamine. Glucuronic Acid. Glycolic Acid**

This is a structured oil-in-water emulsion in the form of a multilamellar. crystalline. liquid phase. which is mainly indicated to deal with the problems associated with the aging of the skin and with dehydration of the skin.

The present formulation has a marked moisturizing effect and, in case of using high doses of glycolic acid, is able to prevent or hinder the formation of wrinkles by means of a marked exfoliating action and chemical peeling.

The action exerted by the glycolic acid also promotes the penetration into the skin both of the acetylglucosamin and of the glucuronic acid, thus making possible a synchronized action that is able to yield appreciable clinical and aesthetic results.

The formation of the multilamellar. crystalline liquid phase inside the emulsion is obtained by means of an accurate calibration of a ternary system (x) and by a pentenary system (y), which are represented by three cetyl or stearyl type emulsifying agents and by five chemical entities of a lipid nature, either solid or liquid, also cetyl or stearyl type, respectively.

The particular method of preparation, together with types of ingredients used, makes it possible to obtain a mesomorphic phase, in which a multilamellar. crystalline liquid phase with the molecular property of the solid phase and the mobility property of the liquid phase is formed on the surface of the oil micelles.

This particular chemical-physical configuration of the emulsion proves to be visible by means of analysis using polarized-light microscopy.

The structured emulsion in the form of a multilamellar. crystalline liquid phase makes it possible to amplify the action of the product over time, to act as a "reservoir" of active ingredients, proves to be useful in the protection of the active ingredients used, and increases the stability of the emulsion.

Thus, the calibrated combination of acetylglucosamine, of glucuronic acid, and of glycolic acid, which are structured in a multilamellar-based. crystalline liquid emulsion, represents an innovation that is able to yield remarkable results.

Water-in-oil Emulsion			
PHASE (A)	Amount in wt. %		
	From	To	
16. STEARETH-2	0.500	4 000 (x)	
17. CETEARYL GLUCOSIDE	0.200	6.000 (x)	
18. PPG-15-STEARYL ETHER	6.000	12.500 (y)	
19. STEARETH-21	0.100	6.400 (x)	
20. CETYL ALCOHOL	0.750	6.100 (y)	
21. STEARIC ACID	0.100	7.500 (y)	
22. CETEARYL ALCOHOL	0.100	5.600 (y)	
23. CETEARYL OCTANOATE	0.200	4.000 (y)	
24. RETINYL PALMITATE (1.000.000 IU/g)	0.050	4.000	
25. TOCOPHERYL ACETATE	0.075	10.000	
<b>PHASE (B)</b>			
26. ACETYLGLUCOSAMINE	0.100	7.900	
27. D-GLUCURONIC ACID GAMMA LACTONE	0.100	7.900	
28. WATER qs.	5.000	5.000	
<b>PHASE (C)</b>			
29. GLYCEROL	0.100	8.750	

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1. Heat phase A) to +80°C and then heat phase C) to +72°C. Combine phas C) with phase A) and homogenize for 15 minutes at 2.500 rpm, under agitation and aspirated vacuum.
2. Initiate a slow cooling with a reduction of 2.5°C every 4 minutes.
3. At +45°C, homogenize at 3.000 rpm for 7 minutes continually under agitation.
5. At +40°C, add phase B) under agitation and allow to cool to a temperature of 30°C, continually under agitation.
5. Upon reaching 30°C, homogenize for 10 minutes at 2.000 rpm.

- Preparation Example 5 (Cosmetic Use)
- 10 Multilamellar-based. Crystalline. Liquid Emulsion Containing Acetylglucosamine. Glucuronic Acid. Retinol. Tocopherol

This is a structured oil-in-water emulsion in the form of a multilamellar, crystalline, liquid phase, which is mainly indicated to deal with the problems associated with the aging of the skin.

The present formulation has a marked antioxidant effect that is able to prevent or hinder the formation of wrinkles.  
 15 The formation of the multilamellar, crystalline liquid phase inside the emulsion is obtained by means of an accurate calibration of a ternary system (x) and by a pentenary system (y), which are represented by three cetyl or stearyl type emulsifying agents and by five chemical entities of a lipid nature, either solid or liquid, also cetyl or stearyl type, respectively.

20 The particular method of preparation, together with types of ingredients used, makes it possible to obtain a mesomorphic phase, in which a multilamellar, crystalline liquid phase with the molecular property of the solid phase and the mobility property of the liquid phase is formed on the surface of the oil micelles.

This particular chemical-physical configuration of the emulsion proves to be visible by means of analysis using polarized-light microscopy.

25 The structured emulsion in the form of a multilamellar, crystalline liquid phase makes it possible to amplify the action of the product over time, to act as a "reservoir" of active ingredients, proves to be useful in the protection of the active ingredients used, and increases the stability of the emulsion.

Thus, the calibrated combination of acetylglucosamine, of glucuronic acid, and of diosmin, which are structured in a multilamellar-based, crystalline liquid emulsion, represents an innovation that is able to yield remarkable results.

Water-in-oil Emulsion			
PHASE (A)	Amount in wt. %		
	From	To	
35	1. STEARETH-2	0.500	4 000 (x)
	2. CETEARYL GLUCOSIDE	0.200	6.000 (x)
	3. PPG-15-STEARYL ETHER	6.000	12.500 (y)
	4 STEARETH-21	0.100	6.400 (x)
	5. CETYL ALCOHOL	0.750	6.100 (y)
	6. STEARIC ACID	0.100	7.800 (y)
	7. CETEARYL ALCOHOL	0.100	5.600 (y)
	8. CETEARYL OCTANOATE	0.200	4 000 (y)
	9. RETINYL PALMITATE (1.000.000 IU/g)	0.050	4.000
	10. TOCOPHERYL ACETATE	0.075	10.000
40	PHASE (B)		
	11. ACETYLGLUCOSAMINE	0.100	7.900
	12. D-GLUCURONIC ACID GAMMA LACTONE	0.100	7.900
45	13. WATER qs.	5.000	5.000
	PHASE (C)		
	14. GLYCEROL	0.100	8.750
50	15. WATER qs.	100	100

Method of Preparation:

(continued)

Preparation for Pharmaceutical or Dietetic Use		
6. LACTOSE	50 mg	
7. MAGNESIUM STEARATE	2 mg	

**Method of Preparation:**

Mix 1.+2.+3.+4.+5.+6.+7. after having provided the various ingredients with equal particle size. Then compress or encapsulate.

While specific embodiments of the invention have been shown and described in detail to illustrate the application of the principles of the invention, it will be understood that the invention may be embodied otherwise without departing from such principles.

**Claims**

1. A composition for cosmetic, pharmaceutical or dietetic use, the composition comprising:  
as an active ingredient, one of active ingredients selected from among a group of chemical substances belonging to sugars, amino sugars, keto sugars, aldo sugars, hydroxylic acids, and polyhydroxy acids and consisting of acetylglucosamine and glucuronic acid, including glucuronolactone as a cyclized form of glucuronic acid.

2. The composition of claim 1, wherein:  
acetylglucosamine are included as the active ingredient in an amount of 0.001 to 30 wt.%.

3. The composition of claim 1, wherein:  
acetylglucosamine is included as the active ingredient in an amount of 0.05 to 15 wt.%.

4. The composition of claim 1, wherein:  
glucuronic acid is included as the active ingredient in an amount of 0.001 to 30 wt.%.

5. The composition of claim 1, wherein:  
glucuronic acid is included as the active ingredient in an amount of 0.05 to 15 wt.%.

6. The composition of claim 1, wherein:  
acetylglucosamine and glucuronic acid are combined as the active ingredients, each in an amount of 0.05 to 10 wt.%.

7. The composition of claim 6, wherein:  
acetylglucosamine and glucuronic acid are combined in equimolar amounts.

8. The composition of claim 2, wherein:

other active ingredients are included such as carboxylic acids, bicarboxylic acids,  $\alpha$ -hydroxy acids,  $\beta$ -hydroxy acids, plants and plant parts, plant extracts, flavonoids, bioflavonoids, isoflavonoids, saponins, chemical substances of a terpene nature, chemical substances of a triterpene nature, amino acids, water-soluble vitamins, and liposoluble vitamins;  
said active and inactive ingredients are formulated for one of internal and external use.

9. The composition of claim 4, wherein:

other active ingredients are included such as carboxylic acids, bicarboxylic acids,  $\alpha$ -hydroxy acids,  $\beta$ -hydroxy acids, plants and plant parts, plant extracts, flavonoids, bioflavonoids, isoflavonoids, saponins, chemical substances of a terpene nature, chemical substances of a triterpene nature, amino acids, water-soluble vitamins, and liposoluble vitamins;  
said active and inactive ingredients are formulated for one of internal and external use.

(continued)

Water-in-oil Emulsion		
PHASE (A)	Amount in wt. %	
	From	To
30. WATER qs.	100	100

## Method of Preparation:

21. Heat phase A) to +80°C and then heat phase C) to +72°C. Combine phase C) with phase A) and homogenize for 15 minutes at 2.500 rpm, under agitation and aspirated vacuum.  
 22. Initiate a slow cooling with a reduction of 2.5°C every 4 minutes.  
 23. At +45°C, homogenize at 3.000 rpm for 7 minutes continually under agitation.  
 24. At +40°C, add phase B) under agitation and allow to cool to a temperature of 30°C, continually under agitation.  
 25. Upon reaching 30°C, homogenize for 10 minutes at 2.000 rpm.

## Preparation for Pharmaceutical Use

Pharmaceutical Form: Vial for intradermal injection		
	From	To
1. ACETYLGLUCOSAMINE	0.0010	2.500
2. GLUCURONIC ACID	0.0005	2.500
3. HYALURONIC ACID	0.0500	50.00
4. PHYSIOLOGICAL WATER qs.	100	100
5. PRESERVATIVE qs.		

## Method of Preparation

Dissolve 1. + 2. + 5. in 4. Add 3. to the solution obtained. Allow to solvate until a clear gel is obtained. Sterilize and then package in vial.

## Preparation for Pharmaceutical Use in Capsules or Tablets

Composition per Unit of Administration	
1. ACETYLGLUCOSAMINE	50 mg
2. GLUCURONIC ACID	50 mg
3. LACTOSE	70 mg
4. MAGNESIUM STEARATE	3 mg

## Method of Preparation:

Mix 1. + 2. + 3. + 4. after having provided the various ingredients with equal particle size. Then compress or encapsulate.

Preparation for Pharmaceutical or Dietetic Use	
1. ACETYLGLUCOSAMINE	15 mg
2. GLUCURONIC ACID	15 mg
3. LEUCOCYANIDIN	90 mg
4. TOCOPHEROL	5 mg
5. SELENIUM	1 mcg

10. The composition of claim 6, wherein:

other active ingredients are included such as carboxylic acids, bicarboxylic acids,  $\alpha$ -hydroxy acids,  $\beta$ -hydroxy acids, plants and plant parts, plant extracts, flavonoids, bioflavonoids, isoflavonoids, saponins, chemical substances of a terpene nature, chemical substances of a triterpene nature, amino acids, water-soluble vitamins, and liposoluble vitamins;

said active and inactive ingredients are formulated for one of internal and external use.

11. The composition of claim 8, wherein:

one of monocarboxylic or bicarboxylic  $\alpha$ -hydroxy acids are included which are selected from among glycolic acid, lactic acid, hydroxybutyric acid, mandelic acid, tartaric acid, malic acid, salicylic acid, hydroxybenzoic acid, and citric acid, either in the dextrorotatory or levorotatory form or in racemic mixture, as well as the corresponding salts or esters, said one of monocarboxylic or bicarboxylic  $\alpha$ -hydroxy acids are include alone or combined in an amount of 0.001 to 50 wt.%.

15 12. The composition of claim 8, wherein:

one of monocarboxylic or bicarboxylic  $\alpha$ -hydroxy acids are included which are selected from among glycolic acid, lactic acid, hydroxybutyric acid, mandelic acid, tartaric acid, malic acid, salicylic acid, hydroxybenzoic acid, and citric acid, either in the dextrorotatory or levorotatory form or in racemic mixture, as well as the corresponding salts or esters, said one of monocarboxylic or bicarboxylic  $\alpha$ -hydroxy acids are include alone or combined in an amount of 0.5 to 15 wt.%.

20 13. The composition of claim 8, further comprising:

vitamin B1 (thiamin), vitamin B2 (riboflavin), vitamin B6 (pyridoxine, pyridoxal), niacin (nicotinic acid, nicotinic amide), pantothenic acid, biotin, folic acid, ascorbic acid, beta carotene, retinol, retinal, retinoic acid, para-aminobenzoic acid, vitamin F (linoleic acid, linolenic acid, arachidonic acid), either in the dextrorotatory or the levorotatory form or in racemic mixture, or in the cis or trans forms, alone or combined, in an amount ranging from 0.001 to 10 wt.%.

25 14. The composition of claim 8, further comprising:

vitamin B1 (thiamin), vitamin B2 (riboflavin), vitamin B6 (pyridoxine, pyridoxal), niacin (nicotinic acid, nicotinic amide), pantothenic acid, biotin, folic acid, ascorbic acid, beta carotene, retinol, retinal, retinoic acid, para-aminobenzoic acid, vitamin F (linoleic acid, linolenic acid, arachidonic acid), either in the dextrorotatory or the levorotatory form or in racemic mixture, or in the cis or trans forms, alone or combined, in an amount ranging from 0.005 to 3 wt.%.

30 15. The composition of claim 8, further comprising:

plants, plant extracts or plant parts or extracts of plant parts, including roots, leaves, fruits, bark, selected from among Vaccinium Myrtillus, Silybum Marianum, Echinacea Angustifolia, Aesculus Hippocastanum, Calendula Officinalis, Centella Asiatica, Hamamelis Virginiana, Citrus Aurantium Amara, Citrus Aurantium Dulcis, Citrus Limonium, Equisetum Arvense, Glycyrrhiza Glabra, Aloe Vera, Ruta Graveolans, Vitis Vinifera, Terminalia S ricea, in the dry, soft or liquid form and in an amount ranging from 0.001 to 30 wt.%.

35 16. The composition of claim 8, further comprising:

plants, plant extracts or plant parts or extracts of plant parts, including roots, leaves, fruits, bark, selected from among Vaccinium Myrtillus, Silybum Marianum, Echinacea Angustifolia, Aesculus Hippocastanum, Calendula Officinalis, Centella Asiatica, Hamamelis Virginiana, Citrus Aurantium Amara, Citrus Aurantium Dulcis, Citrus Limonium, Equisetum Arvense, Glycyrrhiza Glabra, Aloe Vera, Ruta Graveolans, Vitis Vinifera, Terminalia Sericea, in the dry, soft or liquid form and in an amount ranging from 0.25 to 20 wt.%.

40 17. The composition of claim 8, further comprising:

amino acids selected from the group of alanine, arginine, aspartic acid, asparagine, cysteine, glutamic acid, glutamine, glycine, histidine, leucine, isoleucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, the corresponding salts or esters and the various forms reduced to amino alcohols, either in the dextrorotatory or levorotatory form or in racemic mixture, alone or combined, in an amount ranging from 0.001 to 20 wt.%.

45 18. The composition of claim 8, further comprising:

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5 amino acids selected from the group of alanine, arginine, aspartic acid, asparagine, cysteine, glutamic acid, glutamin, glycine, histidin, leucine, isoleucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, the corresponding salts or esters and the various forms reduced to amino alcohols, either in the dextrorotatory or levorotatory form or in racemic mixture, alone or combined, in an amount ranging from 0.05 to 1.5 wt.%.

10 19. The composition of claim 8, further comprising:

10 chemical substances from the group of terpenes, triterpenes, saponins, isoflavonoids, flavonoids, bioflavonoids, selected from among anthocyanidins of the bilberry, escin, madecassic acid, madecassosides, asiaticosides, asiatic acid, rutin and its derivatives, including the salts and esters thereof, diosmin, sericic acid, sericosides, echinacosides, echinacin, glycerretic acid, quercitin, isoquercitin, bisabolene, silymarin, cyanidins, leucocyanidins, although contained in plant extracts or plant parts and the corresponding salts or esters, either in the dextrorotatory or levorotatory form or in racemic mixture, alone or combined, in an amount ranging from 0.001 to 20 wt.%.

15 20. The composition of claim 8, further comprising:

15 one of sulfated or asulfated chemical substances of a polysaccharide nature, such as hyaluronic acid, chitin, dermatan sulfate, heparin and corresponding salts or esters, either in dextrorotatory or levorotatory form or in racemic mixture, alone or combined, in an amount ranging from 0.001 to 20 wt.%.

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(19)



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(12)

## EUROPEAN PATENT APPLICATION

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(54) Composition for cosmetic, pharmaceutical or dietetic use based on an amino-sugar and/ or a polyhydroxylic acid

(57) A composition for cosmetic, pharmaceutical or dietetic use and including as the active ingredient, at least one of the substances which include acetylglucosamine and glucuronic acid in combination with the

active ingredients which belong to the chemical class of the carboxylic acids,  $\alpha$ -hydroxy acids, vitamins, amino acids, and bioflavonoids, and formulated with particular synergists, additives, and excipients for external use or for internal use.

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## PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention EP 97 83 0609  
shall be considered, for the purposes of subsequent  
proceedings, as the European search report

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.CLS)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.CLS)
E	WO 98 06418 A (MCDANIEL H REGINALD ; MANNATECH INC (US); MOORE D ERIC (US); VENNUM) * claims *---	1-10,13, 14,19	A61K7/48 A61K31/00 A61K38/16 A61K31/70
E	GB 2 317 109 A (FARMSENSE) 18 March 1998 * examples *---	1-10,13, 14	
X	EP 0 066 283 A (EUPAN CORP) * example 7 *---	1-10,13, 14	
P,X	WO 97 06810 A (WU GEORGE ; TAM PAUL Y (CA); FRENCH IAN W (CA)) * claims 1,8 *---	1-12	
X	US 4 870 053 A (ZALISZ RENE ET AL) * page 1, column 1, paragraph 2 *---	1-6,8,10 -/-	
INCOMPLETE SEARCH			TECHNICAL FIELDS SEARCHED (Int.CLS)
			A61K
The Search Division considers that the present application, or some or all of its claims, does not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for the following claims:			
Claims searched completely:			
Claims searched incompletely:			
Claims not searched:			
Reason for the limitation of the search: see sheet C			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	23 April 1998	Couckuyt, P	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published-on, or after the filing date L : document cited in the application R : document cited for other reasons B : member of the same patent family, corresponding document	
X : particularly relevant document			
Y : particularly relevant if combined with another document of the same category			
A : technological background			
B : non-patent literature			
P : intermediate document			



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INCOMPLETE SEARCH  
SHEET C

Application Number  
EP 97 83 0689

Claim(s) searched completely:

Claim(s) searched incompletely:  
1-20

Reason for the limitation of the search (non-patentable invention(s)):

In view of the large number of compounds and the different applications covered, as is defined by the general definition of claim 1, the search had to be restricted for economic reasons. The search was limited in view of the obscurity and the specific compound mentioned in the claims and examples.

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Further reason for the limitation of the search:

Claim(s) searched completely:

Claim(s) searched incompletely:  
1-20

Reason for the limitation of the search:

Obscure wording of claim 1. Claim 1 was searched in view of the description and examples.

A composition comprising an active ingredient from the chemical groups (claim 1 and 8) in combination with the active ingredients mixture of acetylglucosamine and glucuronic acid or derivative.



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## PARTIAL EUROPEAN SEARCH REPORT

Application Number

EP 97 83 0609

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int'l Cls)
			TECHNICAL FIELDS SEARCHED (Int'l Cls)
X	PATENT ABSTRACTS OF JAPAN vol. 013, no. 339 (C-624), 31 July 1989 & JP 01 117815 A (POLA CHEM IND INC), 10 May 1989. * abstract *---	1-10	
A	CA 2 019 051 A (MENNEN CO) * claims 1,10,11; examples *---	1-5	
A	FR 2 609 397 A (SEROBIOLOGIQUES LAB SA) * example 9 *---	1-3,8,20	
P,A	WO 97 12597 A (OREAL ; PHILIPPE MICHEL (FR); EBENHAN NAPPE CATHERINE (FR)) * the whole document *---	1-20	
A	DE 24 38 534 A (KOEHLER VALENTIN DR MED) * page 3, paragraph 1; claims *---	1,4,5,8, 10,13,14	
A	DE 27 40 349 A (SCOTT EUGENE J VAN) * page 5, paragraph 3; claim 11 *---	1,4,5, 8-14	
A	EP 0 178 602 A (PERITAIN LTD) * claims *-----	1-3, 8-10,13, 14	